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In This Issue of *Diabetes*

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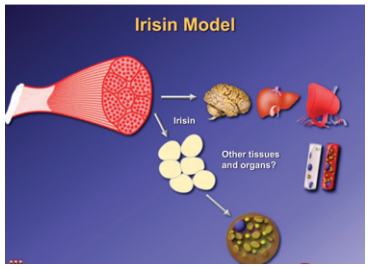
Obesity-Related Loss of Clock Rhythm Differs in Cardiovascular and Metabolic Tissues

Data in this issue of *Diabetes* (**p. 1981**) show differences in the sensitivity of vascular and metabolic tissues to obesity-related loss of diurnal variation. It has been demonstrated in transgenic mouse models that mutation of core clock genes can lead to obesity, and diet-induced obesity (DIO) in wild-type mice has been shown to lead to secondary blunting of rhythmic clock gene transcription in liver and fat tissue. In humans responding to glucose challenge, obesity is associated with blunting of the normal diurnal response. However, no previous studies have looked at the effect of obesity on rhythmic transcription of core clock genes in cardiovascular tissues or upon normal physiological variation in vascular function. Furthermore, the sensitivity of different tissues to clock disruption in disease remains unknown, as does the relationship of insulin resistance and inflammation to the obesity-related loss of clock rhythm. In a DIO mouse model, Prasai et al. looked at the cycling of clock genes *Bmal1* and *Per2*. They found that cycling was impaired in metabolic tissues but not in cardiovascular tissues. Another series of experiments showed that clock rhythm disruption occurs in conjunction with tissue inflammation, but not with insulin resistance. Although studying the effect of obesity on clock genes in humans is difficult due to the need for repeated invasive tissue sampling, these findings suggest that investigation in humans may be warranted. — *Laura Gehl, PhD*

Prasai et al. Diurnal variation in vascular and metabolic function in diet-induced obesity: divergence of insulin resistance and loss of clock rhythm. Diabetes 2013;62:1981–1989

Bruce Spiegelman's 2012 Banting Award Lecture Highlights Irisin

Bruce Spiegelman, PhD, received the American Diabetes Association's Banting Medal for Scientific Achievement at the Association's Scientific Sessions in June 2012 (**p. 1774**). Over the course of >25 years, Dr. Spiegelman and his colleagues have studied various aspects of fat cell biology, including the discovery of several transcriptional components that control fat cell development: PPAR-γ, PGC1-α, and PRDM16. The Spiegelman lab showed that unlike proinflammatory white adipose cells, brown adipose cells work to prevent obesity and diabetes, largely due to their possession of UCP1, a specialized mitochondrial protein. They also demonstrated that suppressing PRDM16 changed the fate of brown fat cells into muscle cells, and the reverse. It is against this backdrop that Dr. Spiegelman's team identified the regulatory hormone irisin, which is induced by exercise. This hormone, which is produced in muscle, was shown to change white fat into more thermogenic beige fat. Further, it induced some of the same benefits that are often seen with exercise, including improved glycemic control. The discovery of irisin may not only deepen our understanding of why exercise is beneficial for health but may also provide a new target for development of therapies for diabetes prevention and treatment. — *Laura Gehl, PhD*



Model of irisin secretion and actions

Spiegelman. Banting Lecture 2012: Regulation of adipogenesis: toward new therapeutics for metabolic disease. Diabetes 2013;62:1774–1782

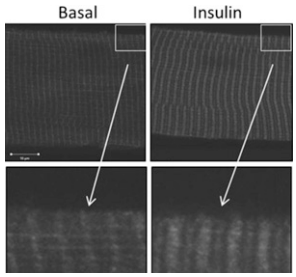
New Approach to Measuring ATP in Diabetes

Mitochondrial function is commonly measured by quantification ATP production using fluorescence or chemiluminescence assays and also by ^{31}P NMR spectrometry. In this issue of *Diabetes* (**p. 1833**), Yu et al. describe a new, highly sensitive, high-throughput ATP assay to measure mitochondrial function. The new assay relies on conversion of 2-deoxyglucose (2DOG) to 2-deoxyglucose phosphate (2DOGP) using the phosphate from ATP, thereby resulting in ADP formation. The extent of 2DOG to 2DOGP conversion depends on ATP produced by the mitochondria. Therefore, mitochondrial respiration or mitochondrial ATP production is measured as a function of 2DOGP formation. Because 2DOG to 2DOGP conversion is rapid and irreversible, the assay can measure respiration as a function of membrane potential at clamped ADP levels. The assay was validated by demonstrating that mitochondria isolated from diabetic muscle produces less 2DOGP (or ATP) compared with control muscle. An added advantage of this technique is its ability to simultaneously measure ROS production using a fluorescent probe. Using the combination of these techniques and muscle mitochondria isolated from control and diabetic rats, the authors show that diabetes results in decreased mitochondrial ATP synthesis, defective state 3 and 4 respiration, and increased ROS production. Overall, the new technique has important implications for sensitively measuring mitochondrial function in different tissues in diabetes and cardiovascular disease. — *Vihang A. Narkar, PhD*

Yu et al. Mitochondrial function in diabetes: novel methodology and new insight. Diabetes 2013;62:1833–1842

New Insight Into Skeletal Muscle Insulin Resistance

In humans, skeletal muscle is responsible for a majority of postprandial glucose uptake. Defects in glucose uptake by muscle play a key role in abnormalities of glucose metabolism, and targeting these defects may offer possibilities for novel therapies. New data published in this issue of *Diabetes* (**p. 1865**) shed light on a key feature of skeletal muscle glucose uptake. In a series of experiments in both mice and humans, Sylow et al. explored the role of the actin cytoskeleton–regulating GTPase Rac1 in skeletal muscle. It is known that insulin actives Rac1, which has been shown to regulate GLUT4 translocation and glucose uptake in cultured muscle. It is also known that Rac1's downstream target, PAK, is involved in cytoskeleton remodeling and GLUT4 translocation. The new experiments show that Rac1 and PAK are activated by insulin in both mice and humans and that Rac1 regulates glucose uptake in mouse muscle. The experiments also show that in insulin-resistant mice and humans, these signals do not function properly. Together, the new data suggest that defects in the Rac1 pathway may be a fundamental feature of insulin resistance and type 2 diabetes and may offer a new target for future therapies. — *Helaine E. Resnick, PhD, MPH*



Insulin-induced redistribution of Rac1 in the myofilaments

Sylow et al. Rac1 signaling is required for insulin-stimulated glucose uptake and is dysregulated in insulin-resistant murine and human skeletal muscle. Diabetes 2013;62:1865–1875

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